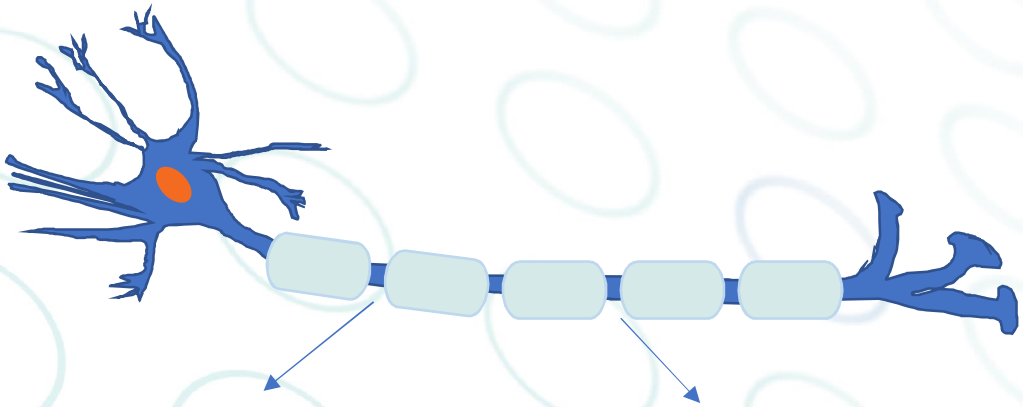
Les Neurofilament light chains, le futur des biomarqueurs neurologiques?

Aurélie Ladang

Department of Clinical Chemistry
University of Liège, CHU Sart-Tilman
Liège, Belgium

aladang@chuliege.be

Neurofilament light chains: NF-L

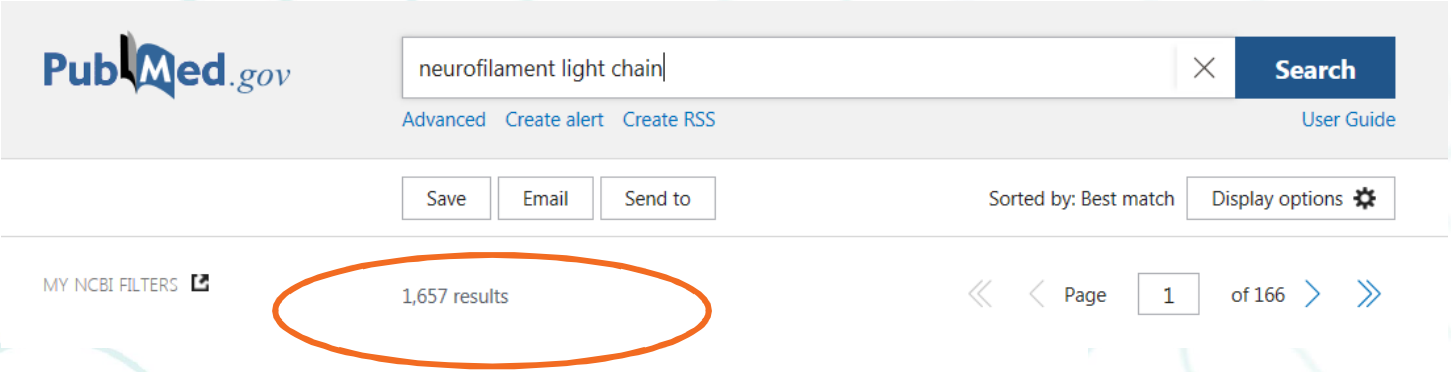


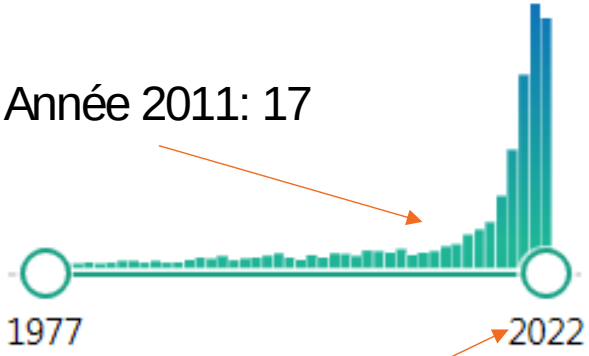
=> Protéine hautement spécifique du système nerveux

Rôle synaptique
Rôle structurel de l
Reflet de la dégénérescence de l
Principalement exprimé dans les neurones à longues gaines de myéline

NF-L: Pourquoi c
où jamais?

Explosion d





NF-L: Pourquoi c où jamais?

Biomarqueurs étudiés précédemment au niveau du LCR

Emergence de nouvelles technologies d immunossay ultrasensibles permettant son dosage au niveau sanguin

Nouvelles technologies d'immunoassays ultrasensibles

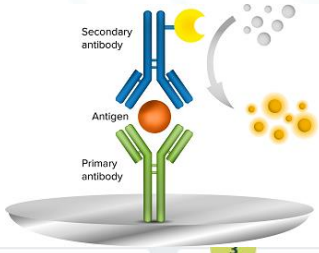
Détection de protéines à des concentrations sub-femtomolaires

SiMoA

Single Molecule Array

Quanterix
The Science of Precision Health

Comment ça marche?

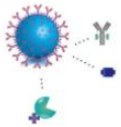


How it works

A high-level look at a Simoa Bead-based assay, from development to data analysis.

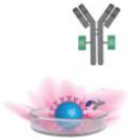
1

Paramagnetic particles coupled with antibodies designed to bind to specific targets are added to the sample.



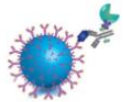
2

Detection antibodies – capable of generating fluorescent product – are added.



3

The objective is to form an immunocomplex consisting of the bead, bound protein, and detection antibody.

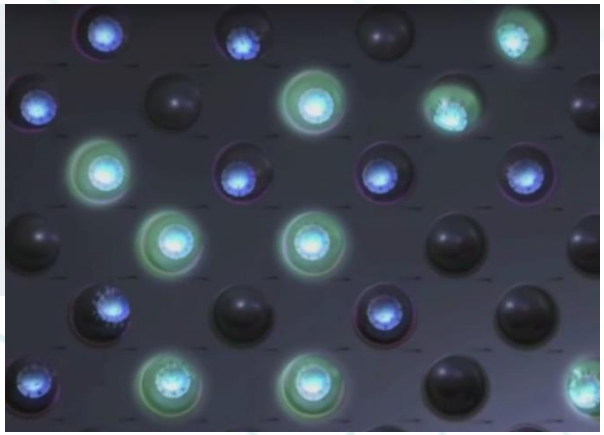


4

At low concentrations, each bead will contain one bound protein, or none.

5

The sample is loaded into arrays, in the Simoa disc, consisting of more than 200,000 microwells – each large enough to hold one bead.



Les analyseurs pourvu de la technologie SiMoA

SR-X

SR-X™ Biomarker Detection System

Offers researchers access to ultra-sensitive biomarker detection capabilities in a compact and affordable system.

1000x	6 in 1	30+
Up to 1000x greater sensitivity	Up to 6 biomarkers in a single assay	Compatible with 30+ assays

HD-X

Delivering Ultrasensitive Biomarker Measurement You Can Count On.

Quanterix is re-engineering ultrasensitivity with the launch of the Simoa® HD-X Analyzer™, the latest model fully automated Simoa bead-based immunoassay platform. Leveraging years of experience with the ground-breaking Simoa HD-1 Analyzer, the new flagship HD-X delivers major productivity improvements, greater user flexibility, unparalleled sensitivity, and best-in-class assay performance across a broad assay menu to empower biomarker research and accelerate drug development.

Ultra-Sensitive Simoa® Bead Technology

Up to 1000x greater sensitivity than traditional immunoassays

Automation

Reproducibility and convenience of sample-answer workflow

Multiplexing

Measure up to 6 biomarkers in a single assay at fg/ml concentrations

NfL dans les compagnies IVD

Siemens => Atellica

Testing service pour compagnies pharmaceutiques
Même anticorps que Quanterix

Neurofilament Light Chain (NfL)*
Testing Service

Fujirebio => Lumipulse

Priorité du service R&D
Anticorps commerciaux

NF-L: Pourquoi c où jamais?

Biomarqueurs étudiés précédemment au niveau du LCR

Emergence de nouvelles technologies d immunossay ultrasensibles permettant son dosage au niveau sanguin

Biomarqueur analytiquement idéale

Spécifique du système nerveux

Stable d -analytique

Variabilité physiologique décrite

Biomarqueurs analytiquement idéal: Contraintes analytiques et pré-analytiques du NF-L

Table 1. Factors influencing preanalytical and analytical variability of blood NfL.

Factor	Type of test	Platform	Number of samples	Influence on NfL levels	References
Freeze-thaw cycles	5 freeze-thaw cycles	ECL	4	-	[12]
	4 freeze-thaw cycles		3	-	[28]
	4 freeze-thaw cycles	SIMOA® HD-1	12	-	[30]
	3 freeze-thaw cycles		6	-	[27]
	1,2,3 freeze-thaw cycles		5	Increase, $P < 0.05$	[29]
Exposure to room temperature	1 to 8 days at 4°C	ECL	4	-	[12]
	1 to 8 days at RT		4	-	[12]
	8 days at RT		3	-	[28]
	1 to 7 days at RT	SIMOA® HD-1	241	-	[25]
	5 days at 4°C		5	Increase, $P < 0.05$	[29]
	5 days at RT		5	Increase, $P < 0.05$	[29]
	3 or 5 days at RT		12	-	[27]
Position-in plate	Sample processing order	SIMOA® HD-1	24	Later processed samples present higher NfL levels	[34]
Serum vs. plasma levels	Correlation	SIMOA® HD-1	16	r: 0.684, $P = 0.009$	[25]
			129	r: 0.96, $P < 0.0001$	[26]
	Comparison absolute values		129	23.1% lower in plasma	[26]
			52	12.0% lower in EDTA plasma	[27]

-, no influence; ECL, electrochemiluminescence; SIMOA® HD-1, single-molecule array analyzer HD-1 (Quanterix, Bellerica, US); RT, room temperature.

Barro et al., Annals of Clinical and Translational Neurology, 2020

Biomarqueurs analytiquement idéal: Contraintes analytiques et pré-analytiques du NF-L

Variabilité biologique

Tableau 4. Données de la variation biologique du NfL, réparties entre les hommes et les femmes
*CV analytique des duplicats

	Nombre de sujets	Nombre total de résultats	Moyenne du nombre d'échantillons par sujet	Nombre de réplicats par échantillon	Valeur moyenne (95% CI), en pg/mL	CVa (95% CI), en %*	CVi normalisé (95% CI), en %	CVg normalisé (95% CI), en %
NfL tous les sujets	20	188	4,65	2	4,63 (4,02-5,25)	7,41 (6,49-8,33)	4,41 (2,94-5,87)	22,97
NfL Hommes	10	92	4,6	2	4,92 (3,88-5,96)	7,64 (6,30-8,98)	3,11 (1,43-4,79)	26,40
NfL Femmes	10	96	4,7	2	4,35 (3,67-5,03)	7,18 (5,87-8,50)	5,89 (3,54-8,25)	18,01

Variations physiologiques du NF-L

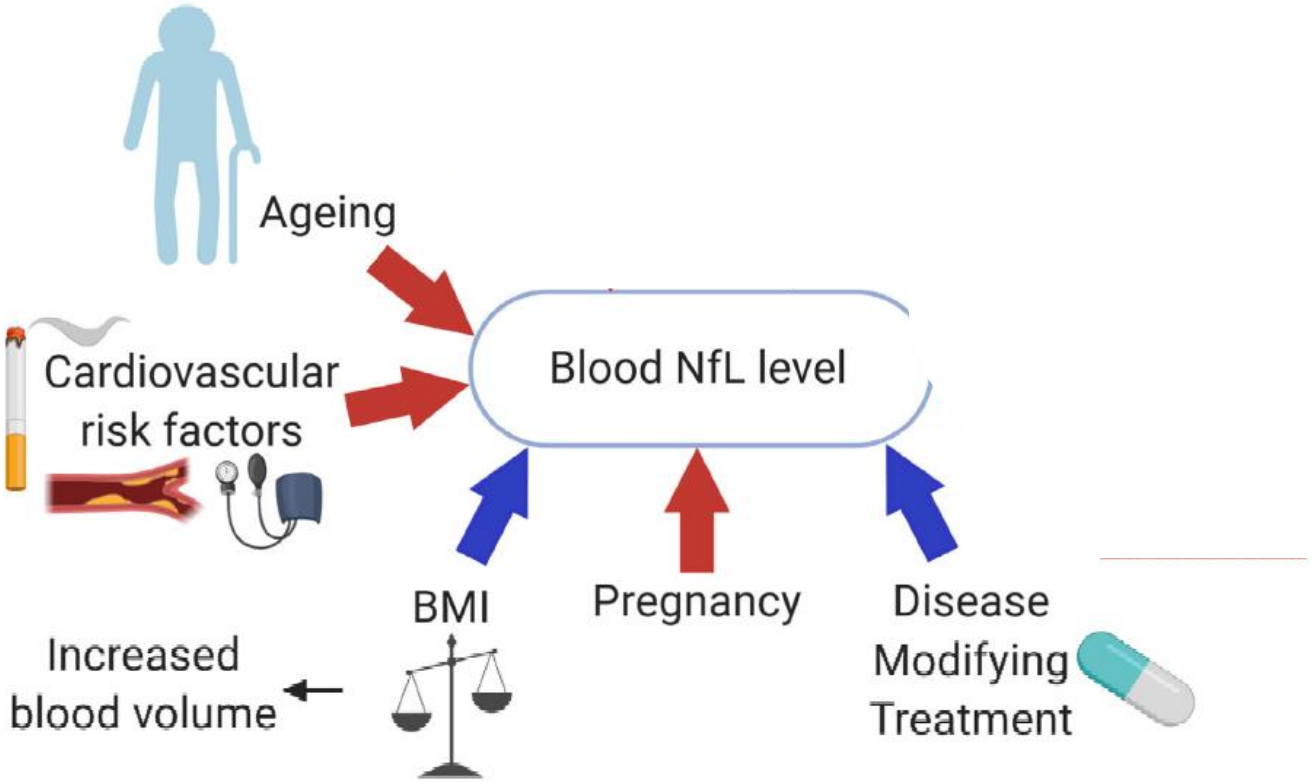


Figure 1. Physiological and pathological factors increasing or decreasing the blood levels of NfL. NfL is released as a consequence of neuronal damage. A rise in NfL (red arrows) is not specific for a specific disease factor and may be caused by both neurodegenerative diseases or a head impact during sports. Cardiovascular risk factors and aging may cause subclinical damage due to silent ischemic events. NfL is not specific for the central nervous system and occurs with injury to the peripheral nervous system. BBB permeability may influence blood NfL levels (light red arrow). Some factors may contribute to a decrease in NfL (blue arrows) including an increase in blood volume associated with BMI. Pregnancy is associated with a physiological increase in NfL. Treatment that decreases neuronal damage results in lower blood NfL levels. BBB, blood–brain barrier; BMI, body-mass-index; CNS, central nervous system; PNS, peripheral nervous system.

Barro et al., Annals of Clinical and Translational Neurology, 2020

Variations physiologiques du NF-L

Etude de l -L chez une large gamme

Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-021-02054-z

ORIGINAL ARTICLE

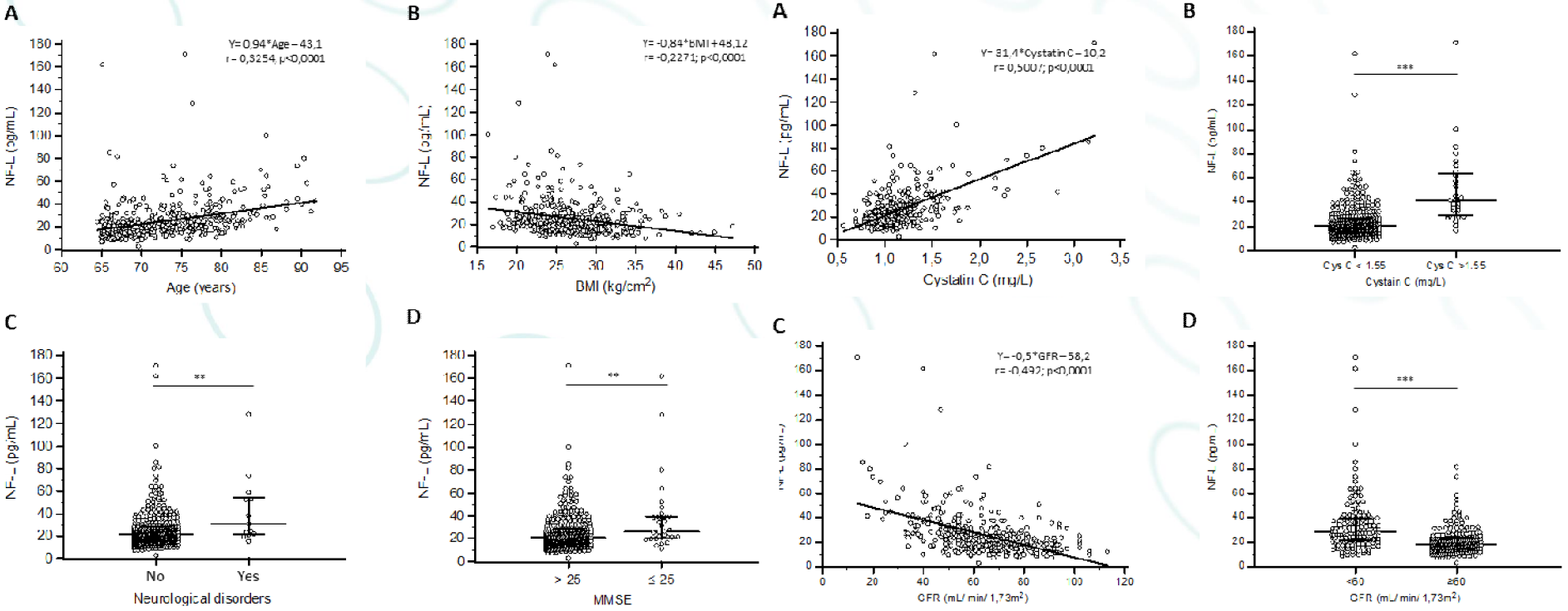
Check for updates

Neurofilament light chain concentration in an aging population

Aurélie Ladang[1] · Stéphanie Kovacs[1] · Laetitia Lengelé[2] · Médéa Locquet[2] · Jean-Yves Reginster[2] · Olivier Bruyère[2,3] · Etienne Cavalier[1]

Cohorte SarcoPhAge
Etude prospective longitudinale chez le sujet âgé vivant à domicile
Pas de critères d
50 kg/m^2
409 séra collectés à l
et 92 ans
Nombreuses données démographiques
Plus de 15 comorbidités auto-raportées

Variations physiologiques du NF-L



Variations physiologiques du NF-L

Variables	n (%)	Median NF-L (IQR)	Mean NF-L (SD)	p-value
Total	409 (100)	21.3 (13.6)	25.5 (17.4)	n.a.
Demographic				
Age				<0.0001 ***
< 70 years	155 (37.9)	17.1 (11.4)	20.7 (16.1)	
70 - 74 years	107 (26.2)	21.0 (10.1)	23.8 (11.1)	
75 - 79 years	91 (22.2)	24.8 (12.9)	29.0 (21.6)	
≥ 80 years	56 (13.7)	30.9 (20.0)	36.6 (17.5)	
Sexe				0.586
M	173 (42.3)	20.8 (12.3)	24.6 (14.3)	
F	236 (57.7)	21.6 (14.5)	26.1 (19.4)	
BMI				0.0008 ***
< 20	23 (5.6)	21.2 (26.7)	32.4 (22.6)	
20 - 24	134 (32.8)	23 (16.5)	29.8 (23.5)	
25 - 29	163 (39.9)	21.7 (12.2)	23.5 (12.3)	
≥ 30	89 (21.8)	18.6 (13.3)	20.9 (10.0)	
Measured comorbidities				
Renal failure				<0.0001 ***
Cystatin C <1.55 mg/L	379 (92.7)	20.7 (12.0)	23.7 (14.4)	
Cystatin C >1.55 mg/L	30 (7.3)	38.3 (33.8)	48.4 (31.3)	
				<0.0001 ***
GFR (CKD-EPI Cys) ≥60	254 (62.1)	18.5 (9.5)	20.3 (9.7)	
GFR (CKD-EPI Cys) <60	155 (37.9)	28.4 (17.7)	34.0 (23.1)	
Self-reported comorbidities				
Number of comorbidities				0.574
0 - 2	102	21.2 (14.4)	25.7 (14.2)	
3 - 5	202	21.4 (12.2)	24.5 (14.9)	
>5	105	21.1 (15.9)	27.2 (23.7)	
Diabetis				0.95
No	342 (83.6)	21.2 (12.8)	25.3 (16.3)	
Yes	67 (16.4)	21.8 (17.2)	26.8 (22.6)	
Cardiovascular disease				0.001 **
No	312 (76.3)	20.8 (12.2)	23.8 (13.8)	
Yes	97 (23.7)	24.6 (18.3)	31.1 (25.2)	
Hypertension				0.194
No	235 (57,5)	21.6 (14.0)	26.6 (18.5)	
Yes	174 (42.5)	20.7 (12.2)	24 (15.7)	
History of fracture				0.029 *
No	183 (44.7)	20.2 (12.1)	23.7 (13.4)	
Yes	226 (55.3)	23.4 (13.5)	27 (20.0)	
Self-reported lifestyle habits				
Smoking				
No	373 (91.2)	21.3 (13.2)	25.1 (16.1)	0.643
Yes	36 (8.8)	21.3 (16.3)	29.8 (27.8)	
Alcohol				0.743
No	204 (49.9)	21.2 (14.3)	25.0 (16.2)	
Yes	205 (50.1)	21.4 (13.5)	26 (18.6)	
Number of drugs				0.1316
0 - 3	108 (26.4)	19.4 (12.5)	24.0 (15.6)	
4 - 6	154 (37.7)	21.6 (13.0)	25.2 (15.2)	
≥7	147 (35.9)	22.8 (14.8)	27.0 (20.6)	
Neurological impairements				
Self-reported neurological troubles				0.007 **
No	396 (96,8)	21.1 (13.2)	24.9 (16.5)	
Yes	13 (3.2)	31.5 (33.1)	43.1 (31.4)	
MMSE				0.001 **
≤25	31 (7.6)	25.9 (18.6)	38.1 (32.6)	
>25	378 (92.4)	21 (12.9)	24.5 (15.2)	
GDS				0.295
<5	274 (67.0)	21 (12.5)	23.9 (13.0)	
5 - 9	98 (24.0)	22.4 (16.3)	28.1 (21.2)	
>9	37 (9.0)	23 (10.0)	30.2 (29.7)	

Ladang et al., under review, 2021

Valeurs de référence

Table 3 NF-L reference ranges according age and renal function

Age	*n*	Mean	Lower limit (95% CI)	Upper limit (95% CI)
GFR ≥ 60 mL/min/1.73 m^2				
≥ 65 years	233	18.2	8.8 (8.2–9.4)	37.7 (35.2–40.4)
≤ 75 years	177	17.4	8.4 (7.7–36.2)	36.2 (33.4–39.2)
> 75 years	56	20.8	10.8 (9.5–12.3)	40.1 (35.3–45.6)
45 ≤ GFR < 60 mL/min/1.73 m^2				
≥ 65 years	95	25.0	10.9 (9.6–12.3)	57.3 (50.6–64.9)
GFR < 45 mL/min/1.73 m^2				
≥ 65 years	36	37.3	12.9 (10.1–16.5)	97.8 (76.4–125.3)

NF-L: Pourquoi c où jamais?

Biomarqueurs étudiés précédemment au niveau du LCR

Emergence de nouvelles technologies d immunossay ultrasensibles permettant son dosage au niveau sanguin

Biomarqueur analytiquement idéale

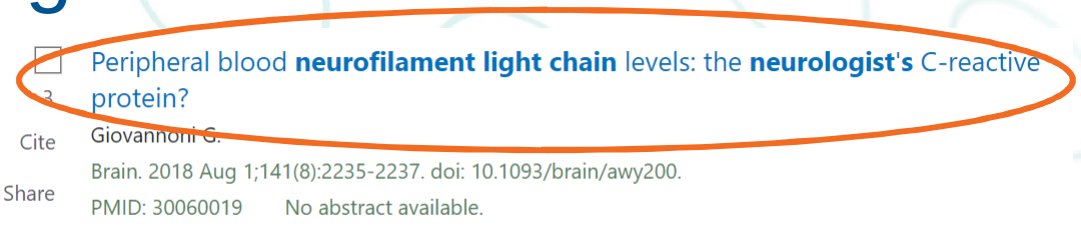
- Spécifique du système nerveux
- Stable d -analytique
- Variabilité physiologique décrite

Absence complète de biomarqueurs au niveau neurologique

NF-L: Pourquoi c où jamais?

Absence complète de biomarqueurs neurologiques au niveau sanguin

Il y a une place pour un biomarqueurs spécifiques des troubles neurologiques au sens large



Peripheral blood **neurofilament light chain** levels: the **neurologist's** C-reactive protein?

Cite

Giovannoni G.

Share

Brain. 2018 Aug 1;141(8):2235-2237. doi: 10.1093/brain/awy200.

PMID: 30060019 No abstract available.

Variations pathologiques du NF-L

Augmenté dans les troubles du système nerveux central dans les maladies

Table 3. Correlation between CSF and blood NfL levels.

Diagnosis	Correlation strength	Blood NfL levels (pg/mL, range/IQR/±SD)	Fluid	Platform	CSF NfL levels (pg/mL, range/IQR/±SD)	Platform	Ref.
HC	*r*: 0.350, *P*: 0.014	-	Serum	Simoa HD-1*	-	Simoa HD-1*	[15]
	r: 0.574, *P*: 0.008	22.0, (12.0 - 36.5)	Serum	ECL	466.5, (338.7 - 651.7)	ECL	[47]
	r: 0.59, *P*: 0.004	11, (8 - 14)	Serum	Simoa HD-1	212, (151 - 289)	ELISA	[44]
	r: 0.772, *P* < 0.0001	-, (2.8 - 53.8)	Serum	Simoa HD-1	-	Simoa HD-1	[27]
	r: 0.39, *P*: 0.029	11.5 (± 6.5)	Serum	Simoa HD-1	1.265 (±551)	NA	[46]
AD	*r*: 0.612, *P* < 0.0001	-	Serum	Simoa HD-1	-	Simoa HD-1	[15]
	r: 0.580, *P* < 0.001	-, (31.0-44.1)	Plasma	Simoa HD-1	-, 1070-2778	ELISA	[88]
	r: 0.568, *P* < 0.001	46.8, (32.7-70.7)	Plasma	Simoa HD-1	608.3 (429.1, 817.7)	ELISA	[93]
	r:0.666, *P* = 0.003	38.1, -	Serum	Simoa HD-1	1595, -	ELISA	[134]
ALS	*r*: 0.781, *P* < 0.001	90, (54.5 - 151.0)	Serum	ECL	7304, (4376 - 11736)	ECL	[47]
	r: 0.79, *P* < 0.0001	179, -	Serum	ECL	-	ELISA	[48]
FTD	*r*: 0.706, *P* < 0.0001	56.9, -	Serum	Simoa HD-1	2948, -	ELISA	[134]
HAD	*r*: 0.89, *P* < 0.0001	114 (46.0 - 235)	Plasma	Simoa HD-1	16185 (1513 - 43010)	ELISA	[13]
HD	*r*:0.868, *P* < 0.0001	31.7 (24.9 - 50.6)	Plasma	Simoa HD-1	1871, (1312 - 2461)	ELISA	[139]
MS	*r*: 0.77, *P* < 0.001	35.9, (22.1 - 61.7)	Serum	Simoa HD-1*	1521, (814 - 2888)	Simoa HD-1*	[32]
	r: 0.79, *P* < 0.0001	16.4 (±14.4)	Plasma	Simoa HD-1	2368 (±1947)	Simoa HD-1	[26]
	r: 0.72, *P* < 0.0001	25.0 (±43.9)	Serum	Simoa HD-1	2368 (±1947)	Simoa HD-1	[26]
	r: 0.63, *P* < 0.001	17, (12 - 22)	Serum	Simoa HD-1	895, (300 - 2060)	ELISA	[44]
PD	*r*: 0.589, *P* < 0.001	9, (4 - 19)**	Plasma	Simoa HD-1	896, -	ELISA	[45]
	r: 0.34, *P*:0.012	10.4, (±4.9)	Serum	Simoa HD-1	1.249, (±666)	NA	[46]
TBI - Boxers	*r*: 0.86, *P*: 0.0003	30, (20-70)**	Serum	Simoa HD-1	845, -	ELISA	20

AD: Alzheimer's Disease; ALS: amyotrophic lateral sclerosis; FTD: frontotemporal dementia; HAD: HIV-associated dementia; HD: Huntington disease; IQR: Interquartile range; MS: multiple sclerosis; -: not available; PD: Parkinson's disease; TBI: traumatic brain injury.
*Basel protocol, the concentrations in blood are ~ 2 fold higher compared to the commercial Simoa NfL kit.
**Concentrations derived from Figure.

Barro et al., Annals of Clinical and Translational Neurology, 2020

Variations pathologiques du NF-L

Augmenté dans les troubles du système nerveux central dans les maladies

Higher than normal levels of NFL in either the blood or CSF were shown to be an indicator of brain damage in multiple chronic and acute neurodegenerative diseases including:

- Alzheimer's disease (AD), both sporadic and familial;
- Amyotrophic lateral sclerosis (ALS);
- Corticobasal degeneration (CBD);
- Creutzfeldt-Jakob disease (CJD);
- Dementia with Lewy bodies (DLB);
- Frontotemporal dementia (FTD);
- HIV-associated dementia (HID);
- Traumatic brain injury (TBI);
- Multiple sclerosis (MS, it includes clinically isolated syndrome, relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis and secondary progressive multiple sclerosis;
- Multiple system atrophy (MSA);
- Normal pressure hydrocephalus (NPH);
- Parkinson's disease (PD) and Parkinson's disease dementia (PDD);
- Spinal muscular atrophy;
- Guillain-Barre syndrome;
- Huntington disease (HD);
- HIV positive with cognitive impairment (HAD);

- Progressive supranuclear palsy (PSP);
- Other disorders, such as bipolar disorder, noninflammatory neurological disorders, optic neuritis, progressive supranuclear palsy (PSP), vascular dementia and stroke.

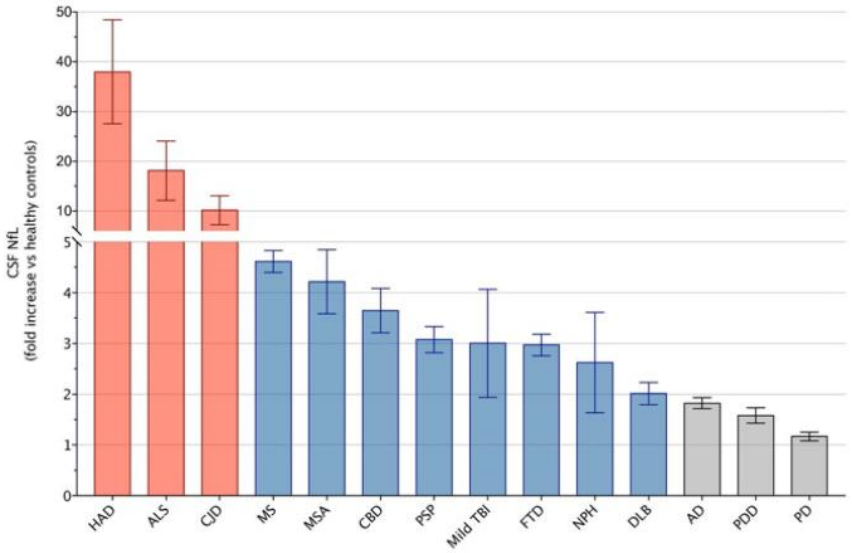
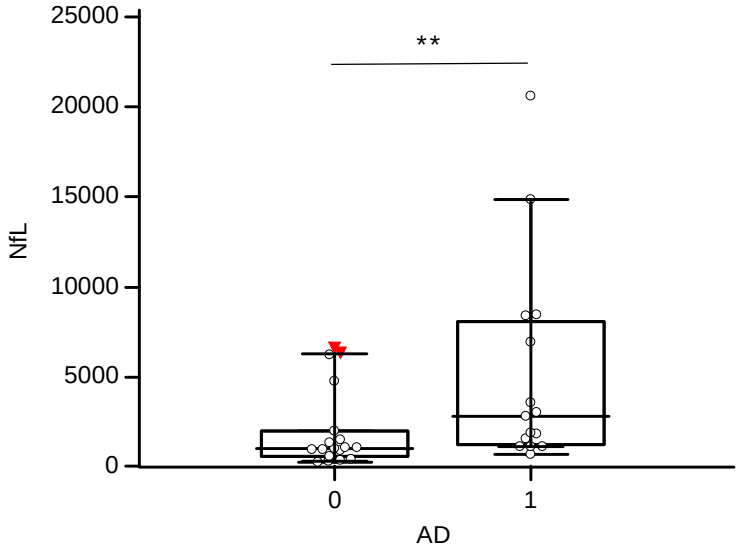


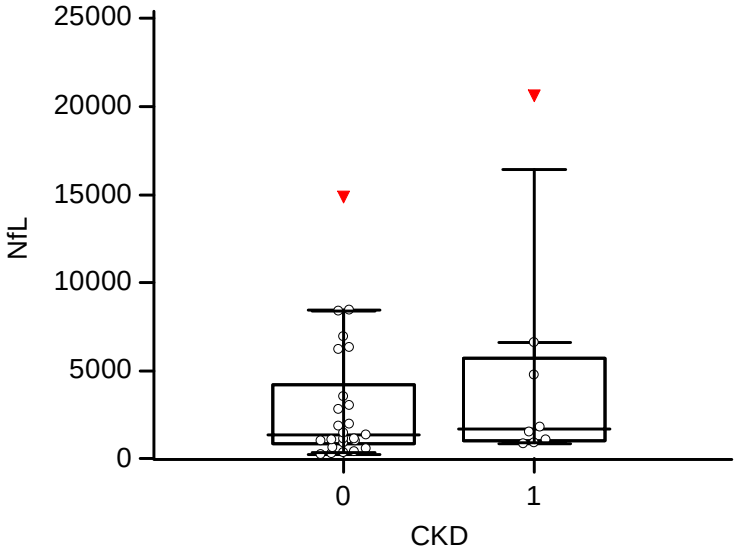
Figure 1: Increase of cerebrospinal fluid (CSF) neurofilament light chain (NfL) with respect to healthy controls (HC) in a variety of central nervous system diseases. Columns represent mean fold increases and SEM of CSF NfL in neurological diseases versus HCs. Red columns: increase of CSF NfL ≥10, blue increase in Nfl 2 -10 fold, grey columns increase in Nfl <2. [6]

Variations pathologiques du NF-L

Augmenté dans les troubles du système nerveux central dans les maladies

Etude sur 33 patients ayant eu une demande de biomarqueurs AD sur LCR





psychologiques

Variations pathologiques du NF-L

Augmenté dans les troubles du système nerveux central dans les maladies neurodégénératives

Augmenté en cas de trauma crânien

(notamment commotions liées à la pratique du sport)

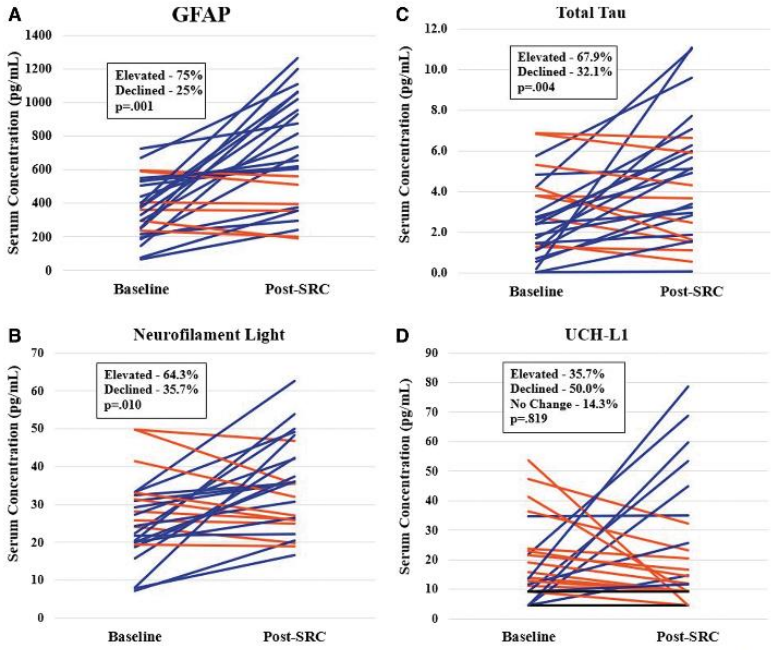


FIG. 1. Serum biomarker concentration changes from baseline to following sport-related concussion (SRC). **(A)** GFAP, **(B)** neurofilament light, **(C)** total tau, and **(D)** UCH-L1. Blue lines show cases of post-SRC elevation, orange lines show cases of post-SRC decline, and black lines show cases of no change in biomarker concentration (UCH-L1 only). To avoid y-axis distortion, the following cases were not included in figures: **(A)** GFAP – 2 cases (1 elevated from 947 to 3677, 1 declined from 2667 to 1571; **(B)** neurofilament light – 2 cases (1 elevated from 6.8 to 87.8, 1 declined from 70.1 to 54.8); **(C)** total tau – 1 case (elevated from 4.4 to 16.2); **(D)** UCH-L1 – 1 case (elevated from 138 to 311). GFAP, glial fibrillary acidic protein; NF-L, neurofilament light chain; T-Tau, total tau; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.

Original Article

Acute Effects of Sport-Related Concussion on Serum Glial Fibrillary Acidic Protein, Ubiquitin C-Terminal Hydrolase L1, Total Tau, and Neurofilament Light Measured by a Multiplex Assay

Breton M. Asken[1,2], Zhihui Yang[3], Haiyan Xu[3], Arthur G. Weber[4], Ronald L. Hayes[4], Russell M. Bauer[2], Steven T. DeKosky[5], Michael S. Jaffee[5], Kevin K.W. Wang[3,*], and James R. Clugston[6,*]

Asken; Journal of neurotrauma ;2020

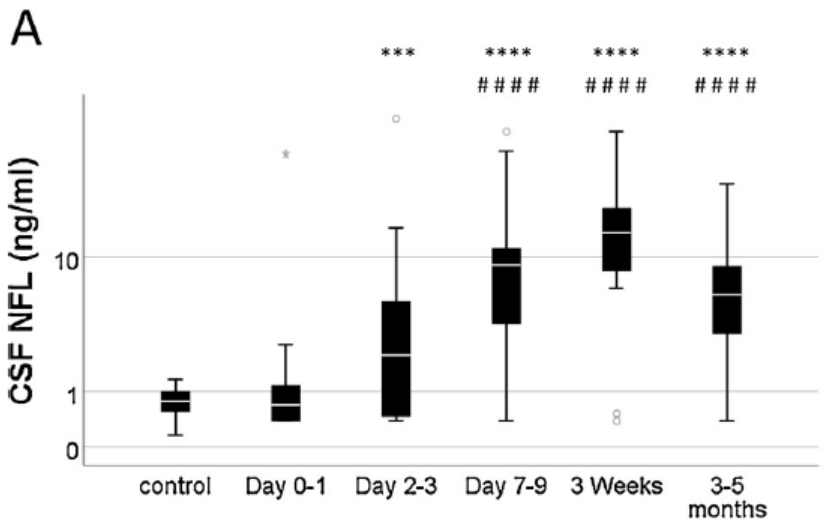
Variations pathologiques du NF-L

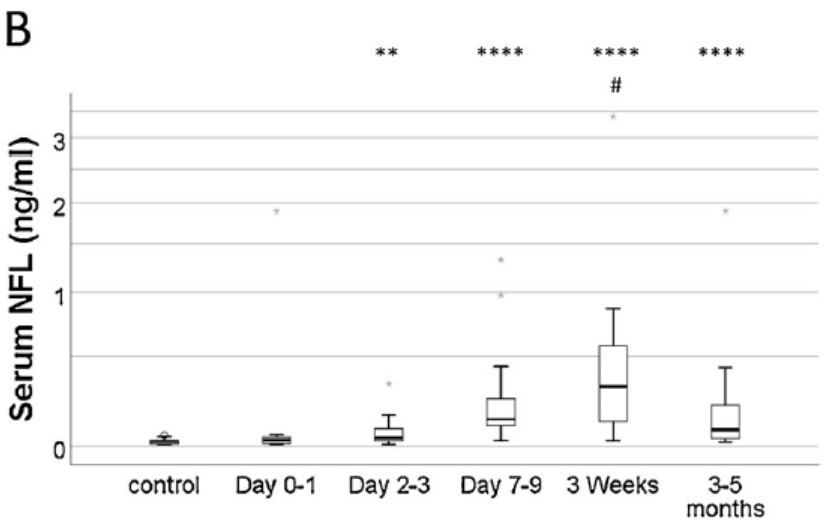
Augmenté dans les troubles du système nerveux central dans les maladies neurodégénératives

Augmenté en cas de trauma crânien

(notamment commotions liées à la pratique du sport)

Augmenté en cas d hypoperfusion cérébrale (AVC)





Pujol-Calderon et al.; Neuroscience letters;2019

NF-L: Pourquoi c
où jamais?

Absence complète de biomarqueurs

A quoi ça sert ?

Positionnement clinique du NF-L

Distinction de troubles psychiatriques et neurologiques

https://doi.org/10.1038/s41467-021-23620-z OPEN

A multicentre validation study of the diagnostic value of plasma neurofilament light

Nicholas J. Ashton[1,2,3,4✉], Shorena Janelidze[5], Ahmad Al Khleifat[6], Antoine Leuzy[5], Emma L. van der Ende[7], Thomas K. Karikari[1], Andrea L. Benedet[8,9], Tharick A. Pascoal[8,9], Alberto Lleó[10,11], Lucilla Parnetti[12], Daniela Galimberti[13,14], Laura Bonanni[15], Andrea Pilotto[16,17], Alessandro Padovani[16], Jan Lycke[18,19], Lenka Novakova[18,19], Markus Axelsson[18,19], Latha Velayudhan[3,20], Gil D. Rabinovici[21,22], Bruce Miller[21], Carmine Pariante[23], Naghmeh Nikkheslat[23], Susan M. Resnick[24], Madhav Thambisetty[25], Michael Schöll[1,2,26], Gorka Fernández-Eulate[27,28], Francisco J. Gil-Bea[27,29], Adolfo López de Munain[27,28,29,30], Ammar Al-Chalabi[6,31], Pedro Rosa-Neto[8,9], Andre Strydom[32,33,34], Per Svenningsson[3,35], Erik Stomrud[5,36], Alexander Santillo[5], Dag Aarsland[3,4,37], John C. van Swieten[7], Sebastian Palmqvist[5,38], Henrik Zetterberg[1,26,39,40], Kaj Blennow[1,39], Abdul Hye[3,4,37,41] & Oskar Hansson[5,36,41✉]

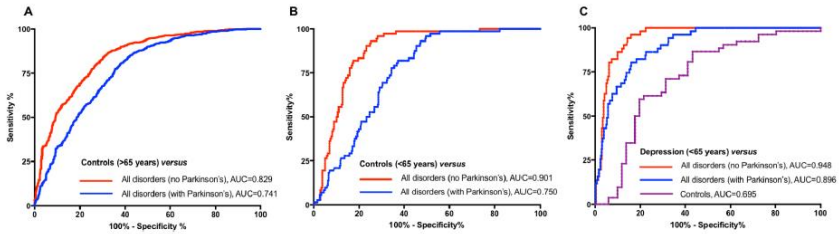


Fig. 4 The diagnsotic accuracy of plasma NfL in identifying neurodegenerative disorders from controls (young/old) and depression. The performance of plasma neurofilament light (NfL) to identify neurodegenerative disorders from controls (CU and SCD) > 65 years of age (**A**), controls (CU and SCD) < 65 years of age (**B**), and depression (**C**).

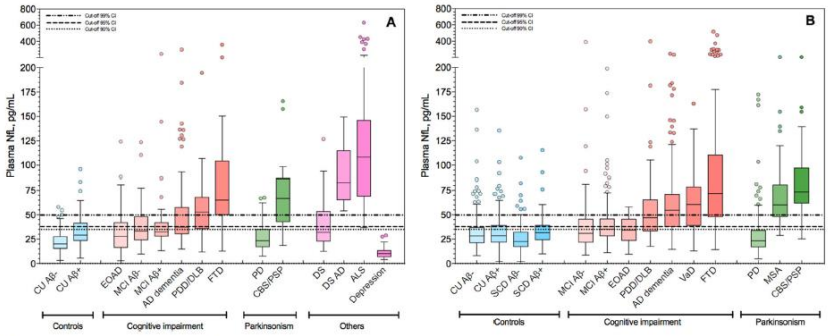


Fig. 1 The concentrations of plasma NfL for different diagnostic and controls groups in the KCL and Lund cohorts. Plasma neurofilament light (NfL) in different diagnostic groups; KCL (**A** $n = 805$) and Lund (**B** $n = 1464$) cohorts. For each plot, the horizontal bar shows the median, and the upper and lower boundaries show the 25th and 75th percentiles, respectively. Source data are provided as a Source Data file. KCL Cohort—AD Alzheimer's disease ($n = 102$), ALS amyotrophic lateral sclerosis ($n = 50$), CU Aβ− cognitively unimpaired without Aβ pathology ($n = 130$), CU Aβ+ cognitively unimpaired with Aβ pathology ($n = 28$), CBS/PSP corticobasal syndrome and progressive supranuclear palsy ($n = 19$), depression ($n = 37$), DS Down syndrome ($n = 29$), DSAD Down syndrome Alzheimer's disease ($n = 12$), EOAD early-onset Alzheimer's disease ($n = 59$), FTD frontotemporal dementia ($n = 54$), MCI Aβ− mild cognitive impairment without Aβ pathology ($n = 55$), MCI Aβ+ mild cognitive impairment with Aβ pathology ($n = 31$), PD Parkinson's disease ($n = 140$), PDD/DLB Parkinson's disease dementia and dementia with Lewy bodies ($n = 59$). Lund Cohort—AD Alzheimer's disease ($n = 134$), CU Aβ− cognitively unimpaired without Aβ pathology ($n = 273$), CU Aβ+ cognitively unimpaired with Aβ pathology ($n = 103$), CBS/PSP corticobasal syndrome and progressive supranuclear palsy ($n = 24$), EOAD early-onset Alzheimer's disease ($n = 23$), FTD frontotemporal dementia ($n = 150$), MCI Aβ− mild cognitive impairment without Aβ pathology ($n = 115$), MCI Aβ+ mild cognitive impairment with Aβ pathology ($n = 165$), MSA multiple system atrophy ($n = 29$), PD Parkinson's disease ($n = 171$), PDD/DLB Parkinson's disease dementia and dementia with Lewy bodies ($n = 46$), SCD Aβ− subjective cognitive decline without Aβ pathology ($n = 134$), SCD Aβ+ subjective cognitive decline with Aβ pathology ($n = 75$), VaD vascular dementia ($n = 22$).

Ashton et al., Nat Commun, 2021

Positionnement clinique du NF-L

Distinction de troubles psychiatriques et neurologiques

diagnostics

MDPI

Review

Neurofilaments as Emerging Biomarkers of Neuroaxonal Damage to Differentiate Behavioral Frontotemporal Dementia from Primary Psychiatric Disorders: A Systematic Review

Vincent Davy [1,2], Julien Dumurgier [1,3], Aurore Fayosse [3], Claire Paquet [1,4] and Emmanuel Cognat [1,4,*]

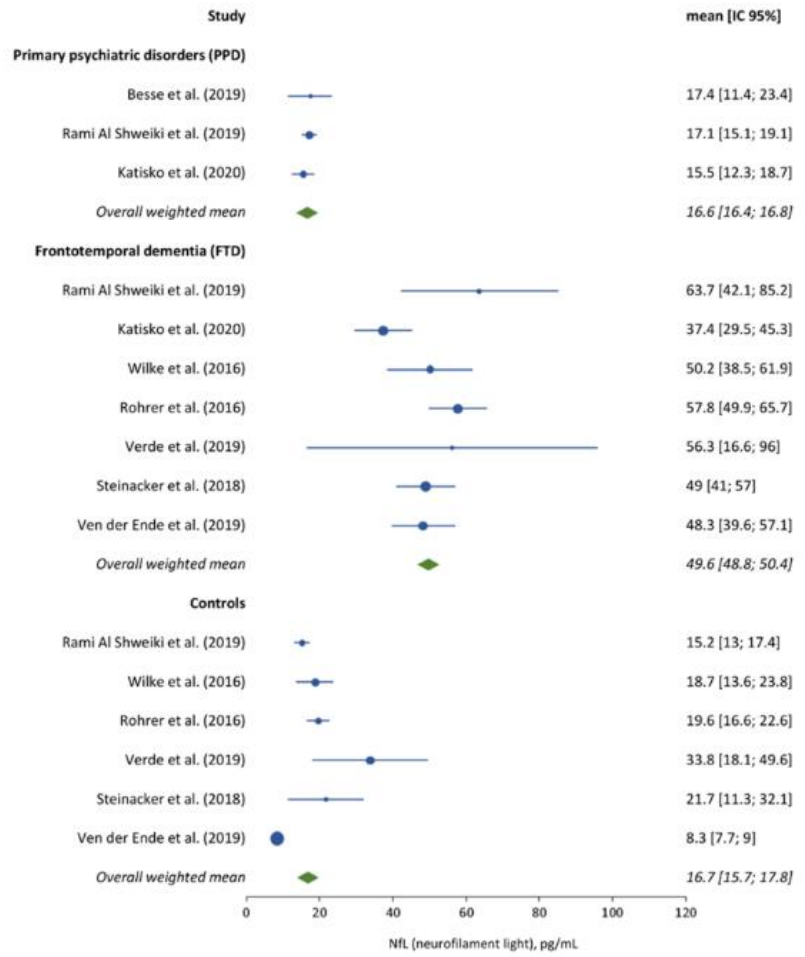


Figure 3. Forest plot analysis of serum NfL levels in FTD, PPD, and control patients.

Positionnement clinique du NF-L

Distinction de troubles psychiatriques et neurologiques

- Mr. H 52 ans
- Référé en neurologie pour difficultés cognitives depuis 2 ou 3 ans
- Consommation éthylique régulière mais sans assuétude
- Trouble de la mémoire, orientation, manque de mots (confirmé par les tests)
- Burn-out il y a 2 ans
- « Choc émotif » ayant empiré la situation cognitive
- Marqueurs Alzheimer non contributifs
- Imagerie: atrophie bitemporale sans autre spécificité

⇒ Diagnostic compliqué par un mélange de facteurs toxiques et de troubles de l

⇒ Plus-value du NF-L?

Positionnement clinique du NF-L

Distinction de troubles psychiatriques et neurologiques

Suivi de l
(sclérose en plaque)

VIEWS & REVIEWS | OPEN ACCESS

Serum neurofilament light as a biomarker in progressive multiple sclerosis

Raju Kapoor, FRCP, Kathryn E. Smith, MS, Mark Allegretta, PhD, Douglas L. Arnold, MD, William Carroll, MBBS, MD, Manuel Comabella, MD, PhD, Roberto Furlan, MD, Christopher Harp, PhD, Jens Kuhle, MD, David Leppert, MD, Tatiana Plavina, PhD, Finn Sellebjerg, MD, PhD, Caroline Sincock, PhD, Charlotte E. Teunissen, PhD, Ilir Topalli, PhD, Florian von Raison, MD, Elizabeth Walker, PhD, and

Correspondence
Dr. Fox
foxr@ccf.org

Table 1 Associations between baseline NfL concentrations and activity of progressive MS

Trial name	Progressive MS subtype and number of subjects	Study design	Correlations between baseline NfL and baseline imaging measures	Correlations between baseline NfL and baseline clinical measures	Correlations between baseline NfL and imaging outcomes	Correlations between baseline NfL and clinical outcomes	Comments
EXPAND and INFORMS[39]	SPMS (n = 1,452) and PPMS (n = 378)	Combined data from phase 3 RCTs (EXPAND and INFORMS)	Gd+ lesion count; T2 lesion volume	EDSS	Brain volume loss after 12 and 24 mo	1. EDSS worsening	Combined treatment and placebo subjects
						2. SDMT worsening (EXPAND study only[53])	
ASCEND[40]	SPMS (n = 365)	Phase 3 RCT	Gd+ lesion count; T2 lesion volume	T25FW, 9HPT	Brain volume loss after 96 wk	Not reported	Placebo data only
ORATORIO	PPMS (n = 516)	Phase 3 RCT	Gd+ lesion count	Not reported	Not reported	EDSS; T25FW; 9HPT	Combined treatment and placebo subjects

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NfL = neurofilament light chain; RCT = randomized controlled trial; SDMT = Symbol Digit Modalities Test; T25FW = Timed 25-Foot Walk time; 9HPT = 9-Hole Peg Test time.

Positionnement clinique du NF-L

Distinction de troubles psychiatriques et neurologiques

Suivi de l (sclérose en plaque)

Table 2 Response of neurofilament light concentrations to treatment in progressive MS

Study reference	MS phenotype	Study design (treatment duration)	Treatment	Subjects for NfL analysis	NfL biofluid (assay used)	Change in NfL concentration	Comments
Axelsson et al.[45]	SPMS and PPMS	Observational phase 2A, with age-matched controls (12–24 mo)	Rituximab (n = 5) or mitoxantrone (n = 30)	30 SPMS, 5 PPMS, and 14 healthy controls	CSF (Uman Diagnostics NF-light ELISA)[14]	Mean NFL concentration was reduced 51%, from 1,780 ng/L to 870 ng/L (p = 0.007) irrespective of MS phenotype or treatment	1. NfL concentration was only reduced in either previously untreated patients or those with enhancing lesions at baseline.
							2. There was no correlation between NfL concentrations at different time points and pre- and posttreatment EDSS or MSSS
Romme Christensen et al.[46]	SPMS and PPMS	Phase 2A single-arm (60 wk)	Natalizumab	7 SPMS and 10 PPMS	CSF (Uman Diagnostics NF-light ELISA)[14]	Mean NfL concentration was reduced by 37%, from 657 ng/mL to 414 ng/mL (p = 0.03)	1. Changes in NfL concentrations correlated with changes in MTR in NAWM and GM. 2. Combined data from this trial and a phase 2A trial of methylprednisolone in SPMS and PPMS[54] found a correlation between CSF NfL and changes in the MS Impact Scale
Ratzer et al.[48]	SPMS and PPMS	Phase 2A single-arm (60 wk)	Methylprednisolone	14 SPMS and 11 PPMS	CSF (Uman Diagnostics NF-light ELISA)[14]	Mean NfL concentration not reduced by treatment (baseline 827 pg/mL vs final 434 pg/mL, p = 0.067)	Treatment-associated changes in EDSS, MSFC, 9HPT, T25FW, MSIS, MTR, and DTI measures
INFORMS	PPMS	Phase 3 randomized trial (24 mo)	Fingolimod or placebo	170 fingolimod and 119 placebo	EDTA plasma (Quanterix Simoa NF-light® Advantage Kit)[19]	NfL levels lower in fingolimod-treated patients than placebo at mo 24 (p = 0.0012)	No significant difference between groups at mo 12
EXPAND[49]	SPMS	Phase 3 randomized trial (>21 mo)	Siponimod or placebo	380 siponimod and 145 placebo	EDTA plasma (Quanterix Simoa NF-light® Advantage Kit)[19]	Plasma NfL levels increased by 9.2% with placebo and decreased by 5.7% with siponimod (p = 0.0004)	
ASCEND[40]	SPMS	Phase 3 randomized trial (96 wk)	Natalizumab or placebo	379 natalizumab and 365 placebo	Serum (Quanterix Simoa NF-light® Advantage Kit)[19]	sNfL at wk 48 and 96 was lower in natalizumab vs placebo (ratios: 0.84, p < 0.001, and 0.80, p < 0.001, respectively)	1. Week 96 sNfL was higher in those with progression on the multicomponent disability endpoint. 2. Differences in sNfL were observed in those with and without Gd+ lesions at baseline, relapses in 2 y before study and on-study inflammatory activity (Gd + lesions, new T2 lesions, or relapse).
SPRINT[52]	SPMS and PPMS	Phase 2 randomized trial (96 wk)	Ibudilast or placebo	Serum: 119 ibudilast and 120 placebo. CSF: 30 ibudilast and 28 placebo	CSF and serum (Quanterix Simoa NF-light® Advantage Kit)[19]	No between-group differences in change in NfL in either serum or CSF	Concurrent anti-inflammatory therapy was only injectibles or none; ongoing focal inflammatory activity may have confounded assessment of ibudilast's effect on NfL
ORATORIO[50]	PPMS	Phase 3 randomized trial (96 wk)	Ocrelizumab or placebo	347 ocrelizumab 169 placebo	Serum (Quanterix Simoa NF-light® Advantage Kit)[19]	NfL was 15.7% lower with ocrelizumab vs 0.2% lower with placebo (p < 0.001)	For patients with BL NfL above 90th percentile of healthy controls, a higher proportion decreased into normal range with ocrelizumab (40.4%) vs placebo (16.6%) (p < 0.001)

Abbreviations: DTI = Diffusion Tensor Imaging; GM = Gray Matter; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSIS = Multiple Sclerosis Impact Scale; MSSS = Multiple Sclerosis Severity Score; MTR = Magnetization Transfer Ratio; NAWM = Normal Appearing White Matter; NfL = neurofilament light chain; PPMS = Primary Progressive Multiple Sclerosis; Simoa = single molecule array; sNfL = serum NfL; SPMS = Secondary Progressive Multiple Sclerosis; T25FW = Timed 25-Foot Walk time; 9HPT = 9-Hole Peg Test time.

Positionnement clinique du NF-L

Distinction de troubles psychiatriques et neurologiques

Suivi de l
(sclérose en plaque)

PLOS ONE

RESEARCH ARTICLE

Neurofilament light chain in blood as a diagnostic and predictive biomarker for multiple sclerosis: A systematic review and meta-analysis

Study	MS N	MS Mean	MS SD	Control N	Control Mean	Control SD	SMD with 95% CI	Weight (%)
MS vs. HC								
Hakansson (2018)	41	17	7.68	22	11	4.75	0.88 [0.34, 1.42]	8.27
Hogel (2018)	79	26.74	16.9	13	24.89	7.37	0.12 [-0.47, 0.70]	7.50
Jakimovski (2019)	127	22.3	13.35	52	15.38	11.59	0.54 [0.21, 0.87]	12.98
Sejbaek (2019)	52	16.4	14.4	23	7.3	3	0.75 [0.24, 1.25]	8.92
Baldassari (2019)	22	13.98	4.12	10	6.27	3.01	2.02 [1.12, 2.91]	4.13
Manouchehrinia (2020)	3,092	12.19	7.13	1,026	7.78	3.04	0.69 [0.62, 0.77]	18.91
Bridel (2020)	89	13.56	8.59	88	7.1	2.9	1.01 [0.69, 1.32]	13.37
Saraste (2020)	79	22.62	12.08	10	24.13	6.02	-0.13 [-0.79, 0.53]	6.48
Cruz-Gomez (2021)	35	44.48	27.7	23	33.28	16.47	0.47 [-0.06, 1.00]	8.40
Heterogeneity: τ^2 = 0.06, I^2 = 66.68%, H^2 = 3.00							0.67 [0.45, 0.90]	
Test of $\theta_i = \theta_j$: Q(8) = 24.01, p = 0.00								
MS vs. NINDC								
Thebault (2020)	67	10.06	7.61	37	7.26	4.62	0.42 [0.01, 0.82]	11.04
Heterogeneity: τ^2 = 0.00, I^2 = .%, H^2 = .							0.42 [0.01, 0.82]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .								
Overall							0.64 [0.44, 0.85]	
Heterogeneity: τ^2 = 0.06, I^2 = 65.03%, H^2 = 2.86								
Test of $\theta_i = \theta_j$: Q(9) = 25.73, p = 0.00								
Test of group differences: $Q_b(1)$ = 1.16, p = 0.28								

Random-effects DerSimonian-Laird model

Fig 2. Forest plot of blood Nfl. concentrations between MS patients *vs.* age-matched controls. Nfl.: neurofilament light chain; MS: multiple sclerosis; HC: healthy control; NINDC: non-inflammatory neurological disease control; SMD: standard mean difference.

Study	MS N	MS Mean	MS SD	Control N	Control Mean	Control SD	SMD with 95% CI	Weight (%)
PMS vs. HC								
Novakova (2017)	82	40.25	62.69	42	14.84	13.77	0.49 [0.11, 0.87]	4.62
Barro (2018)	68	43.24	18.03	258	24.48	9.62	1.58 [1.29, 1.88]	4.93
Hogel (2018)	33	35.26	20.23	13	24.89	7.37	0.59 [-0.07, 1.24]	3.50
Ferraro (2019)	70	12.94	4.54	10	9.57	3.96	0.75 [0.08, 1.43]	3.42
Watanabe (2019)	11	32.17	14.67	49	18.9	8.71	1.33 [0.63, 2.02]	3.34
Jakimovski (2019)	42	28.82	14.89	52	15.38	11.59	1.02 [0.59, 1.45]	4.40
Bridel (2020)	33	13.65	6.98	88	7.1	2.9	1.49 [1.05, 1.93]	4.36
Saraste (2020)	23	32.55	17.38	10	24.13	6.02	0.56 [-0.19, 1.32]	3.12
Heterogeneity: τ^2 = 0.19, I^2 = 76.09%, H^2 = 4.18							1.01 [0.65, 1.36]	
Test of $\theta_i = \theta_j$: Q(7) = 29.28, p = 0.00								
RRMS vs. HC								
Kuhle (2016)	31	12.88	18.26	18	2.27	4.26	0.72 [0.12, 1.31]	3.72
Novakova (2017)	204	66.84	269.65	42	14.84	13.77	0.21 [-0.12, 0.54]	4.78
Barro (2018)	178	31.1	15.7	258	24.48	9.62	0.53 [0.34, 0.73]	5.23
Hogel (2018)	46	20.62	10.6	13	24.89	7.37	-0.43 [-1.05, 0.19]	3.63
Ferraro (2019)	21	9.74	2.31	10	9.57	3.96	0.06 [-0.70, 0.81]	3.12
Watanabe (2019)	38	26.8	17.57	49	18.9	8.71	0.59 [0.16, 1.03]	4.39
Jakimovski (2019)	85	19.13	10.56	52	15.38	11.59	0.34 [-0.01, 0.69]	4.73
Sejbaek (2019)	52	16.4	14.4	23	7.3	3	0.75 [0.24, 1.25]	4.10
Olsson (2020) cohort 1	49	9.33	6.49	58	5.08	2.66	0.88 [0.49, 1.28]	4.53
Olsson (2020) cohort 2	68	11.82	4.92	50	6	2.14	1.46 [1.05, 1.87]	4.49
Bridel (2020)	56	13.5	9.41	88	7.1	2.9	1.02 [0.66, 1.37]	4.70
Saraste (2020)	56	19.65	9.13	10	24.13	6.02	-0.51 [-1.19, 0.17]	3.40
Szilasiova (2021)	159	8.58	4.34	66	6.49	2.52	0.54 [0.24, 0.83]	4.93
Liu (2021)	98	18.15	14.48	84	4.78	2.07	1.25 [0.93, 1.57]	4.84
Cruz-Gomez (2021)	35	44.48	27.7	23	33.28	16.47	0.47 [-0.06, 1.00]	3.98
Niiranen (2021)	63	15.77	7.3	14	11.3	5.58	0.64 [0.05, 1.22]	3.76
Heterogeneity: τ^2 = 0.15, I^2 = 78.97%, H^2 = 4.76							0.58 [0.36, 0.80]	
Test of $\theta_i = \theta_j$: Q(15) = 71.33, p = 0.00								

Random-effects DerSimonian-Laird model

Fig 3. Forest plot of blood NfL concentrations between PMS *vs.* HC and RRMS *vs.* HC. PMS: progressive MS; RRMS: relapsing-remitting MS.

Study	PMS N	PMS Mean	PMS SD	RRMS N	RRMS Mean	RRMS SD	SMD with 95% CI	Weight (%)
Novakova (2017)	82	40.25	62.69	204	66.84	269.65	-0.12 [-0.37, 0.14]	11.87
Barro (2018)	68	43.24	18.03	178	31.1	15.7	0.74 [0.45, 1.03]	11.60
Hogel (2018)	33	35.26	20.23	46	20.62	10.6	0.95 [0.48, 1.42]	9.74
Ferraro (2019)	70	12.94	4.54	21	9.74	2.31	0.77 [0.27, 1.27]	9.43
Watanabe (2019)	11	32.17	14.67	38	26.8	17.57	0.32 [-0.36, 0.99]	7.69
Jakimovski (2019)	42	28.82	14.89	85	19.13	10.56	0.80 [0.41, 1.18]	10.67
Ayrignac (2020)	18	13.63	6.66	111	9.33	4.52	0.88 [0.37, 1.39]	9.34
Huss (2020)	39	20.79	11.16	47	17.04	13.38	0.30 [-0.13, 0.73]	10.20
Bridel (2020)	33	13.65	6.98	56	13.5	9.41	0.02 [-0.41, 0.45]	10.17
Saraste (2020)	23	32.55	17.38	56	19.65	9.13	1.07 [0.55, 1.58]	9.30
Overall							0.56 [0.27, 0.85]	
Heterogeneity: τ^2 = 0.17, I^2 = 79.79%, H^2 = 4.95								
Test of $\theta_i = \theta_j$: Q(9) = 44.52, p = 0.00								
Test of θ = 0: z = 3.78, p = 0.00								

Random-effects DerSimonian-Laird model

Fig 4. Forest plot of blood Nfl. levels between PMS *vs.* RRMS.

https://doi.org/10.1371/journal.pone.0274565.g004

Study	Relapse N	Relapse Mean	Relapse SD	Remission N	Remission Mean	Remission SD	SMD with 95% CI	Weight (%)
Kuhle (2016)	26	12.72	19.14	5	13.32	26.95	-0.03 [-0.99, 0.93]	9.87
Novakova (2017)	86	23.5	19.53	346	18.04	10.42	0.43 [0.19, 0.67]	23.81
Abdelhak (2018)	18	16.8	7.24	24	6.55	15.29	0.82 [0.18, 1.45]	15.16
Thebault (2020)	18	13.24	6.84	49	9.36	4.62	0.73 [0.18, 1.29]	16.87
Ayrignac (2020)	18	8.95	5.09	93	9.4	4.43	-0.10 [-0.60, 0.41]	17.96
Liu (2021)	15	52.92	66.97	83	15.84	13.04	1.31 [0.73, 1.89]	16.32
Overall							0.54 [0.16, 0.92]	
Heterogeneity: τ^2 = 0.14, I^2 = 68.95%, H^2 = 3.22								
Test of $\theta_i = \theta_j$: Q(5) = 16.10, p = 0.01								
Test of θ = 0: z = 2.80, p = 0.01								

Random-effects DerSimonian-Laird model

Fig 5. Forest plot of blood Nfl. levels between MS in relapse *vs.* MS in remission.

Positionnement clinique du NF-L

Distinction de troubles psychiatriques et neurologiques

Suivi de l)

Diagnostic de certaines pathologies (ALS)

Biomarkers

Neurofilament light chain as a biological marker for amyotrophic lateral sclerosis: a meta-analysis study

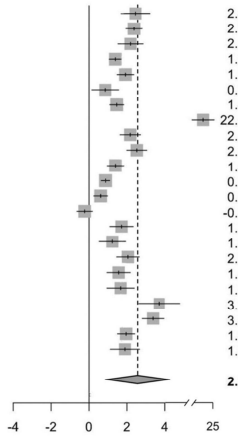
Giacomo Sferruzza, Luca Bosco, Yuri Matteo Falzone, Tommaso Russo, Teuta Domi, Angelo Quattrini, ...show all

Pages 446-457 | Received 14 Jul 2021, Accepted 07 Nov 2021, Published online: 07 Dec 2021

Download citation https://doi.org/10.1080/21678421.2021.2007952 Check for updates

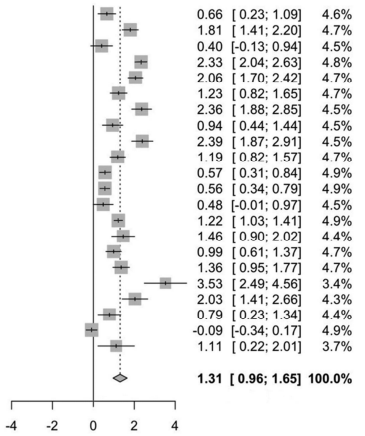
Study (ALS - HC)	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight
Gagliardi et al, 2021	32	4334.00	2010.0000	18	272.60	347.6000	2.45	[1.69; 3.22]	4.4%
Delaby et al, 2020	46	2955.67	1978.9505	118	440.33	168.1185	2.38	[1.95; 2.81]	4.4%
Sun et al, 2020	45	6555.00	3094.5914	19	755.67	327.5964	2.19	[1.53; 2.86]	4.4%
Huang et al, 2020	108	2218.00	1976.1573	79	112.00	113.2704	1.39	[1.07; 1.72]	4.4%
Abu Rumeileh et al, 2020	80	6258.00	3607.0000	43	603.00	286.0000	1.93	[1.48; 2.37]	4.4%
Yang et al, 2020	19	151.12	9.8800	15	141.22	12.8000	0.86	[0.15; 1.57]	4.4%
Olsson et al, 2019	68	4615.00	3973.3388	75	570.33	286.4796	1.46	[1.09; 1.84]	4.4%
Andrés Benito et al, 2018	85	4637.55	192.3100	21	610.40	81.1000	22.66	[19.51; 25.80]	3.8%
Ill´an Galan et al, 2018	38	3174.00	1825.8925	49	507.67	185.5941	2.18	[1.64; 2.72]	4.4%
Pawlitski et al, 2018	50	14556.00	7249.9405	50	1487.50	517.5345	2.52	[1.99; 3.05]	4.4%
Schreiber et al, 2018	89	11314.00	8270.0000	33	1318.00	491.0000	1.40	[0.96; 1.84]	4.4%
Skillbäck et al, 2017	715	2800.00	2945.0000	107	395.00	372.0000	0.87	[0.67; 1.08]	4.4%
Gaiani et al, 2017	94	12267.90	22395.4000	44	809.50	1065.3000	0.61	[0.25; 0.98]	4.4%
Steinacker et al, 2017	125	2267.67	1771.5206	28	2973.33	6147.7178	-0.23	[-0.64; 0.18]	4.4%
Weydt et al, 2016 (Umea cohort)	45	5595.67	3676.5982	19	208.53	114.3784	1.72	[1.10; 2.34]	4.4%
Weydt et al, 2016 (Ulm cohort)	19	7760.67	8479.0599	19	208.53	114.4585	1.23	[0.53; 1.93]	4.4%
Wilke et al, 2016	25	7100.33	4899.8742	46	1044.00	456.8575	2.06	[1.46; 2.65]	4.4%
Lu et al, 2015	38	7805.33	5670.2821	20	485.63	249.7258	1.57	[0.95; 2.18]	4.4%
Menke et al, 2015	25	7118.00	4879.0000	17	663.00	464.0000	1.67	[0.95; 2.39]	4.4%
Pijnenburg et al, 2015	15	20287.67	8106.9640	24	1332.00	557.9447	3.71	[2.63; 4.79]	4.3%
Gaiottino et al, 2013	49	5662.33	2422.6527	68	326.00	68.1663	3.39	[2.81; 3.96]	4.4%
Zetterberg et al, 2007	79	3818.75	2184.0174	40	296.25	135.6455	1.96	[1.50; 2.42]	4.4%
Rosengren et al, 1996	12	1743.00	1661.0000	34	138.00	31.0000	1.90	[1.13; 2.67]	4.4%
Random effects model	**1901**			**986**			**2.58**	**[0.86; 4.30]**	**100.0%**

Heterogeneity: I^2 = 95%, τ^2 = 17.4731, p < 0.01



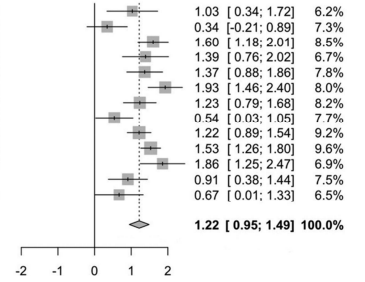
Study (ALS - OND)	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight
Gagliardi et al, 2021	32	4334.00	2010.0000	67	3087.10	1812.4617	0.66	[0.23; 1.09]	4.6%
Delaby et al, 2020	46	2955.67	1978.9505	116	978.00	348.3199	1.81	[1.41; 2.20]	4.7%
Sun et al, 2020	45	6555.00	3094.5914	20	5300.33	3006.2838	0.40	[-0.13; 0.94]	4.5%
Olsson et al, 2019	68	4615.00	3973.3388	397	990.00	374.2469	2.33	[2.04; 2.63]	4.8%
Feneberg et al, 2018	128	8939.25	4498.6009	65	1313.30	640.6586	2.06	[1.70; 2.42]	4.7%
Ill´an Galan et al, 2018	38	3174.00	1825.8925	86	1419.33	1191.3174	1.23	[0.82; 1.65]	4.7%
Gong et al, 2018	80	3645.25	1667.6353	40	396.75	143.5292	2.36	[1.88; 2.85]	4.5%
Li et al, 2018	53	3138.00	2076.5535	25	1284.00	1648.4897	0.94	[0.44; 1.44]	4.5%
Pawlitski et al, 2018	50	14556.00	7249.9405	50	2130.50	774.7415	2.39	[1.87; 2.91]	4.5%
Scarafino et al, 2018	85	5991.00	3237.2600	51	2223.55	2982.4100	1.19	[0.82; 1.57]	4.7%
Rossi et al, 2018	190	5000.00	3500.0000	82	2900.00	4003.0000	0.57	[0.31; 0.84]	4.9%
Skillbäck et al, 2017	715	2800.00	2945.0000	87	1214.00	1252.0000	0.56	[0.34; 0.79]	4.9%
Gaiani et al, 2017	94	12267.90	22395.4000	20	2398.60	1256.9000	0.48	[-0.01; 0.97]	4.5%
Poesen et al, 2017	220	32033.25	19620.4198	316	14379.75	9267.2512	1.22	[1.03; 1.41]	4.9%
Wilke et al, 2016	25	7100.33	4899.8742	41	2494.67	1080.9153	1.46	[0.90; 2.02]	4.4%
Oeckl et al, 2016	57	5603.20	4823.6000	66	1777.26	2715.8000	0.99	[0.61; 1.37]	4.7%
Steinacker et al, 2016	253	12146.50	6803.1642	28	3288.00	2207.5463	1.36	[0.95; 1.77]	4.7%
Pijnenburg et al, 2015	15	20287.67	8106.9640	25	2393.33	904.0358	3.53	[2.49; 4.56]	3.4%
Gaiottino et al, 2013	49	5662.33	2422.6527	20	1415.33	456.3679	2.03	[1.41; 2.66]	4.3%
Tortelli et al, 2012	37	5167.25	2195.1632	21	3302.75	2587.1787	0.79	[0.23; 1.34]	4.4%
Zetterberg et al, 2007	79	3818.75	2184.0174	206	4044.75	2801.0727	-0.09	[-0.34; 0.17]	4.9%
Rosengren et al, 1996	12	1743.00	1661.0000	11	346.00	176.0000	1.11	[0.22; 2.01]	3.7%
Random effects model	**2371**			**1840**			**1.31**	**[0.96; 1.65]**	**100.0%**

Heterogeneity: I^2 = 94%, τ^2 = 0.6239, p < 0.01



Study (ALS - ALSmd)	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight
Brodovitch et al, 2021	20	43527.00	34120.0000	17	11196.00	26100.0000	1.03	[0.34; 1.72]	6.2%
Sun et al, 2020	45	6555.00	3094.5914	18	5150.33	5820.2519	0.34	[-0.21; 0.89]	7.3%
Abu Rumeileh et al, 2020	80	6258.00	3607.0000	46	1583.00	675.0000	1.60	[1.18; 2.01]	8.5%
Kasai et al, 2019 (discovery cohort)	29	10100.50	6932.4000	21	2307.54	2384.4000	1.39	[0.76; 2.02]	6.7%
Kasai et al, 2019 (validation cohort)	41	8932.10	6104.3000	39	2543.80	2154.8000	1.37	[0.88; 1.86]	7.8%
Feneberg et al, 2018	128	8939.25	4498.6009	27	958.80	930.3598	1.93	[1.46; 2.40]	8.0%
Scarafino et al, 2018	85	5991.00	3237.2600	30	1971.00	3229.3900	1.23	[0.79; 1.68]	8.2%
Gaiani et al, 2017	94	12267.90	22395.4000	18	1082.30	633.0000	0.54	[0.03; 1.05]	7.7%
Poesen et al, 2017	220	32033.25	19620.4198	50	10006.00	8020.2244	1.22	[0.89; 1.54]	9.2%
Steinacker et al, 2016	253	12146.50	6803.1642	85	2974.50	2014.2562	1.53	[1.26; 1.80]	9.6%
Gaiottino et al, 2013	49	5662.33	2422.6527	20	1547.00	1458.4625	1.86	[1.25; 2.47]	6.9%
Tortelli et al, 2012	37	5167.25	2195.1632	25	3033.00	2490.5601	0.91	[0.38; 1.44]	7.5%
Reijn et al, 2009	28	62.00	64.0000	14	24.00	32.0000	0.67	[0.01; 1.33]	6.5%
Random effects model	**1109**			**410**			**1.22**	**[0.95; 1.49]**	**100.0%**

Heterogeneity: I^2 = 71%, τ^2 = 0.1784, p < 0.01



Positionnement clinique du NF-L

Distinction de troubles psychiatriques et neurologiques

Suivi de l)

Diagnostic de certaines pathologies (ALS)

Diagnostic de certaines pathologies en combinaison avec les biomarqueurs

Published in final edited form as:

Alzheimers Dement. 2021 May ; 17(5): 822–830. doi:10.1002/alz.12233.

ATN incorporating cerebrospinal fluid neurofilament light chain detects frontotemporal lobar degeneration

Katheryn A.Q. Cousins[1], Jeffrey S. Phillips[1], David J. Irwin[1], Edward B. Lee[2], David A. Wolk[2], Leslie M. Shaw[2], Henrik Zetterberg[3,4,5,6], Kaj Blennow[3,4], Sarah E. Burke[1], Nikolas G. Kinney[1], Garrett S. Gibbons[2], Corey T. McMillan[1], John Q. Trojanowski[2], Murray Grossman[1]

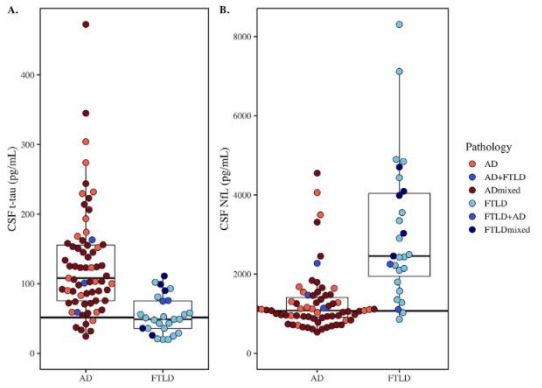


FIGURE 2.

Boxplots of total tau (t-tau) and neurofilament light chain (NfL) in autopsy-confirmed Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD). Comparisons across pathology groups of (Panel A) cerebrospinal fluid (CSF) t-tau and (Panel B) CSF NfL. Shape indicates N status (−/+). Horizontal black lines indicate optimal cut-points. Patients above the line are considered N+; patients below are N−. Color indicates pathological subtype: AD (light red; negligible copathology), AD+FTLD (royal blue), AD_{mixed} (dark red), FTLD (light blue), FTLD+AD (royal blue), $FTLD_{mixed}$ (dark blue)

Positionnement clinique du NFL

Prédiction de l -AVC)

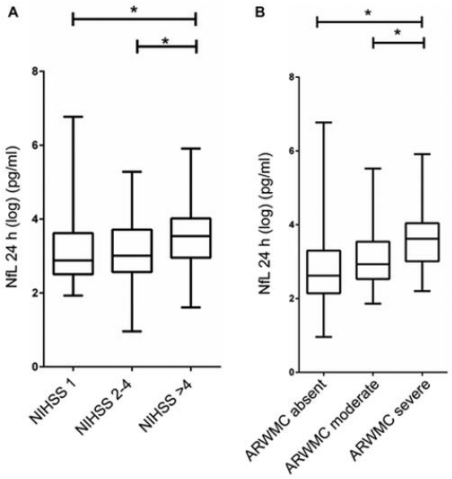
et neurologiques

NfL (Neurofilament Light Chain) Levels as a Predictive Marker for Long-Term Outcome After Ischemic Stroke

Timo Uphaus, Stefan Bittner, Sonja Gröschel, Falk Steffen, Muthuraman Muthuraman, Katrin Wasser, Mark Weber, Rolf Wachter, Klaus Gröschel

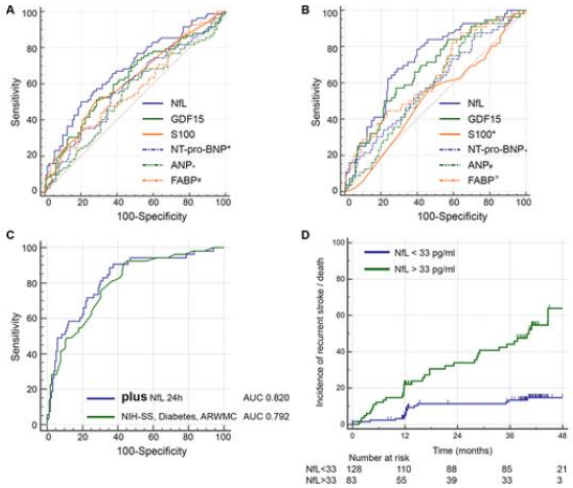
Originally published 20 Sep 2019 | https://doi.org/10.1161/STROKEAHA.119.026410 | Stroke. 2019;50:3077–3084

is related to



Download figure | Download PowerPoint

Figure 2. sNfL values are associated with stroke severity and age-related white matter changes. **A**, Patients divided into 3 groups with regard to National Institutes of Health Stroke Scale (NIHSS) tertials at admission. NfL (neurofilament light chain) measured 24 h after admission is steadily increasing with severity of neurological deficits. NIHSS 1: median, 2.880 (interquartile range [IQR], 2.51–6.78); NIHSS 2 to 4, 3.01 (2.51–3.62); NIHSS >4, 3.54 (2.96–4.02); ANOVA *P*=0.004. **B**, White matter lesions as rated by age-related white matter changes (ARWMCs), NfL 24 h for absent group: 2.62 (2.14–3.30); moderate, 2.93 (2.53–3.54); severe, 3.62 (3.01–4.04); ANOVA *P*<0.001. Box=median+IQR; whisker=minimum to maximum. **P*<0.05.



Download figure | Download PowerPoint

Figure 3. sNfL is superior to other biomarkers for prediction of recurrent stroke or death. **A**, Receiver operating characteristic (ROC) curves concerning unfavorable functional outcome (modified Rankin Scale score, ≥2) under consideration of different biomarkers. Comparison of ROC area under the curve (AUC) compared with serum NfL (neurofilament light chain; sNfL), **P*=0.0164, +*P*=0.0027, #*P*=0.0288. **B**, ROCs concerning occurrence of the cardiovascular end point (recurrent stroke/death) under consideration of different biomarkers. Comparison of ROC-AUC compared with sNfL, **P*=0.0017, +*P*=0.0012, #*P*=0.0015, °*P*=0.0479. **C**, ROC to predict the cardiovascular end point (recurrent stroke/death) for the combination of National Institutes of Health Stroke Scale (NIHSS), diabetes mellitus, and ARMWC-rating (green) exhibited an area under the curve (AUC) of 0.729 (95% CI, 0.663–0.788; *P*<0.001). The additional use of sNfL (blue) showed a trend (*P*=0.052) toward an independent improvement of AUC to 0.820 (95% CI, 0.761–0.870; *P*<0.001). **D**, Time to cardiovascular end point (recurrent stroke/death), patients divided by Youden index of ROC curve analysis in patients with high NfL levels (>33 pg/mL, green) and low NfL levels (<33 pg/mL, blue), nonlogarithmic-transformed values, log-rank test for differences between the groups, *P*<0.001. This incidence curve was computed from competing risk analysis. ANP indicates atrial natriuretic peptide; ARWMC, age-related white matter changes; FABP, fatty acid–binding proteins; GDF15, growth differentiation factor 15; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Positionnement clinique du NF-L

Prédiction de l -AVC)

Distinction de troubles psychiatriques et neurologiques

Suivi de l)

logies (ALS)

logies en combinaison avec les

frontiers | Frontiers in Neurology

SYSTEMATIC REVIEW
published: 16 May 2022
doi: 10.3389/fneur.2022.841898

Temporal Patterning of Neurofilament Light as a Blood-Based Biomarker for Stroke: A Systematic Review and Meta-Analysis

Jasmin D. Sanchez[1†], Richard A. Martirosian[2†], Katherine T. Mun[3], Davis S. Chong[3], Irene Lorenzo Llorente[3], Timo Uphaus[4], Klaus Gröschel[4], Teresa A. Wölfer[5], Steffen Tiedt[5], Jason D. Hinman[3] and the DEMDAS Study Group*

OPEN ACCESS

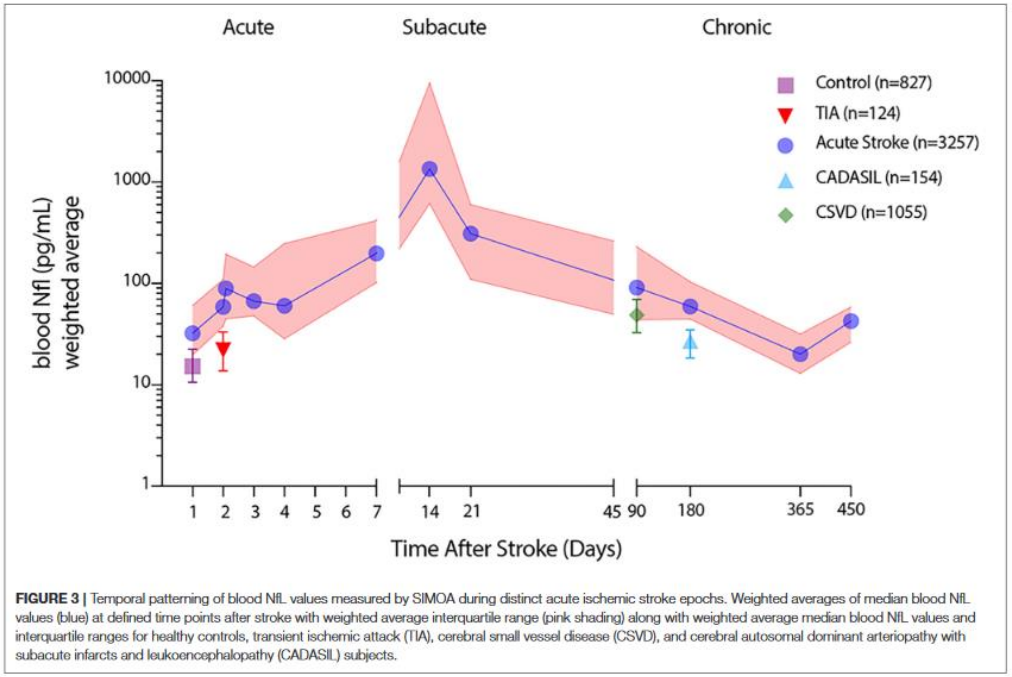


FIGURE 3 | Temporal patterning of blood NfL values measured by SIMOA during distinct acute ischemic stroke epochs. Weighted averages of median blood NfL values (blue) at defined time points after stroke with weighted average interquartile range (pink shading) along with weighted average median blood NfL values and interquartile ranges for healthy controls, transient ischemic attack (TIA), cerebral small vessel disease (CSVD), and cerebral autosomal dominant arteriopathy with subacute infarcts and leukoencephalopathy (CADASIL) subjects.

Positionnement clinique du NF-L

- Distinction de troubles psychiatriques et neurologiques
- Suivi de l)
- Diagnostic de certaines pathologies (ALS)
- Diagnostic de certaines pathologies en combinaison avec les biomarqueurs d'Alzheimer (FTD)
- Prédiction de l -AVC)

Le plus made-in CHU ;-)

NF-L et la sarcopénie

2018 EWGSOP definition

Low muscle strength	Low muscle quality or quantity	Low physical performance
Hand grip strength	Skeletal muscle mass index	Short performance battery test (SPPB test)
JAMAR dynamometer	DXA Appendicular lean mass / height^2	Balance Walking speed Chair stand test

NF-L et la sarcopénie

Maladie musculaire ou dégénérescence neuromusculaire?

Physical performance:

- An objectively measured whole-body function related to locomotion
- Multidimensional concept that not only involves muscles but also central and peripheral nervous function, including balance

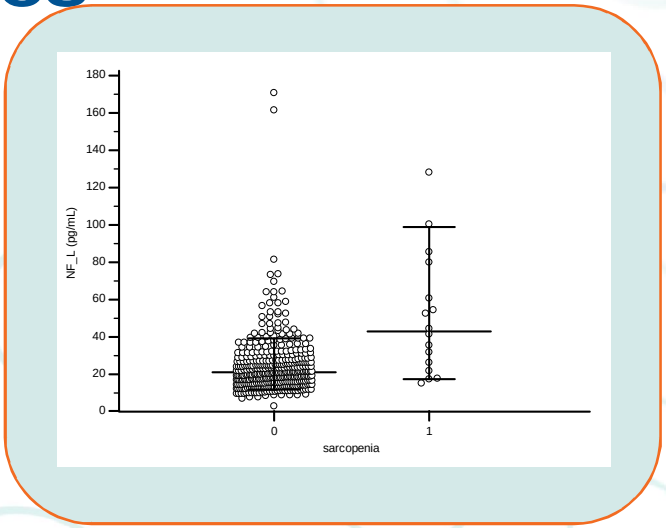
According to « Sarcopenia: revised European consensus on definition and diagnosis »
Age Ageing. 2019 Jan; 48(1): 16 31

Muscle strength:

- Disability or decline of functional capacities are associated with loss of muscle strength rather than loss of muscle mass

NF-L et la sarcopénie

NF-L est augmenté chez les patients sarcopéniques



Univariate

	Controls (n=393)	EWGSOP2 (n=16)	p-value
Age (years)	72 (68 - 77)	78 (74 - 87)	0.0003 ***
Women	221 (56)	8 (50)	0.8281
Number of drugs	5 (3 - 8)	6 (5 - 10)	0.0408 *
Number of concomitant diseases	4 (2 - 6)	5.5 (3.5 - 7.5)	0.0481 *
MMSE	29 (28 - 29)	28 (26 - 29)	0.175
Body mass index (kg/m^2)	26.5 (23.9 - 29.9)	22.6 (20.0 - 24.3)	<0.0001 ***
NF-L (pg/mL)	21.1 (15.4 - 28.3)	43.0 (24.1 - 70.3)	0.0001 **

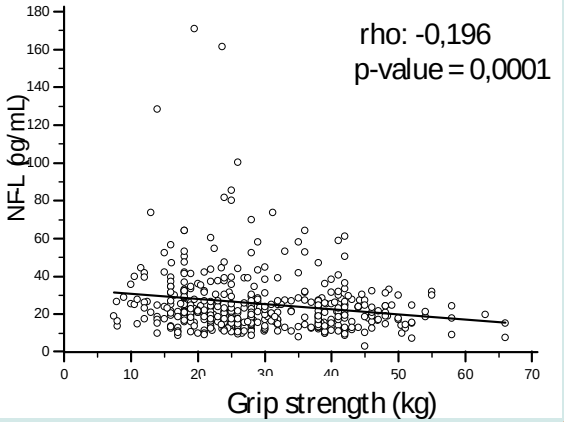
Logistic

Dependent variable: Sarcopenic (EWGSOP definition)	Odds Ratio (95%CI)	p-value
Age (years)	1.13 (1.05 - 1.22)	0.0021 **
Sexe	1.70 (0.51 - 5.70)	0.3899
Number of drugs	0.95 (0.77 - 1.17)	0.6183
Number of concomitant diseases	1.15 (0.90 - 1.47)	0.2624
MMSE	1.41 (0.26 - 7.73)	0.6914
Body mass index (kg/m^2)	6.99 (1.04 - 46.72)	0.045 *
NF-L (pg/mL)	1.02 (1.01 - 1.04)	0.0198 *

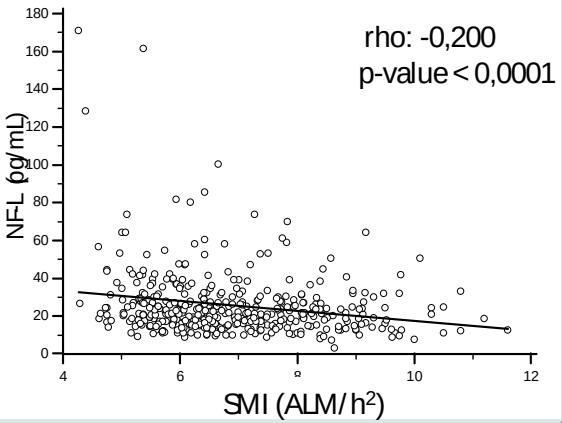
NF-L et la sarcopénie

Parmi les 3 critères de la sarcopénie, seule la performance physique est indépendamment associée au NF-L

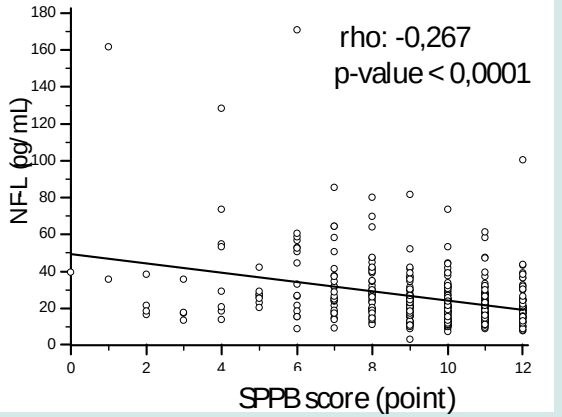
Muscle strength



Muscle mass



Physical performance



Multiple linear regression model

Dependent variable: NF-L	$r_{-partial}$	p-value
Age	0.1174	0.0187 *
BMI	-0.1892	0.0001 ***
Renal function	0.5303	<0.0001 ***
MMSE	-0.0527	0.2921
Muscle strength	0.0329	0.5106
Muscle mass	-0.0498	0.3201
Physical performance	-0.2032	<0.0001 ***

Conclusions

Les plus

- Spécifique des dommages neuronaux

Les moins

- Non spécifique d
- Dépendant de
  - La fonction rénale (sous-estimé dans la littérature!!!)
  - L'âge
  - Le BMI

Qu -ce qu

- Des kits labélisés et automatisables

Merci pour votre attention

Les Neurofilament light chains,
le futur des biomarqueurs neurologiques?